J. Chem. Thermodynamics 97 (2016) 261–263

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

What is the enthalpy of formation of pyrazine-2-carboxylic acid?

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ARTICLE INFO

Article history:
Received 2 February 2016
Accepted 3 February 2016
Available online 10 February 2016

Keywords:
Pyrazine-2-carboxylic acid
Enthalpy of formation
Quantum chemical calculations
G3(MP2)//B3LYP method
Homodesmotic reactions

ABSTRACT

There are two contemporary conflicting, indeed, incompatible determinations of measurements of the enthalpies of combustion and of formation of pyrazine-2-carboxylic acid in the literature, (-2268.0 ± 0.9 and -271.2 ± 1.1 kJ · mol^{-1}) and (-2211.4 ± 0.9 and -327.8 ± 1.1 kJ · mol^{-1}). The current paper discusses these two sets of values and from the use of a measurement of the enthalpy of sublimation, a newly evaluated enthalpy of formation of pyrazine itself, and of the quantum chemical calculations at the G3(MP2)//B3LYP level, the former results are accepted and the derived gas phase enthalpy of formation, $-(167.6 \pm 3.1)$ kJ · mol^{-1}, suggested.

1. Introduction

Pyrazine-2-carboxylic acid (also occasionally called pyrazinoic acid) is a comparatively simple heterocyclic derivative. It has but one substituent on a 1-ring, 6-membered aromatic species with but two non-carbon atoms. This species has long been known with multiple applications. Adapting the approach from the old, pioneering study by Gabriel and Sonn [1], Hall and Spoerri reported a particularly simple synthesis of pyrazine-2-carboxylic acid some 75 years ago [2]. This was part of a study to synthesize 2-aminopyrazine and its derivatives. This synthesis made use of pyrazine-2,3-dicarboxylic acid where we recognize that two years earlier, Spoerri and Erickson [3] studied the 2,5-dicarboxylic acid isomer and its transformation into the corresponding diamino counterpart and derivatives.

For many years through the present, pyrazine-2-carboxylic acid, accompanied by its salts and acyl derivatives, has been known to have interesting and important properties. Indeed, the last calendar year (2015) saw the publication of mixed metal pyrazine-2-carboxylate salts (including an assemblage that contains 30 cations, 24 heterocyclic anions, among other constituents), that were reported [4] to have novel magnetocaloric properties associated with novel nanosized metallorings. Pyrazine-2-carboxylic acid, as its amide, is among the most effective medicines against tuberculosis. Yet in a contemporaneous review [5], it was acknowledged that the *in vivo* therapeutic form, the acid itself, still lacks a molecular mechanism for its activity. Combining both the material and medicinal chemical concerns, aerosols containing pyrazine-2-carboxylate salts (with protonated L-leucine and ammonium counterions) have been suggested with improved anti-tubercular activity [6].

Pyrazine-2-carboxylic acid has also attracted the interest of thermochemists. Ribeiro da Silva and her co-workers [7] measured the enthalpies of combustion and of sublimation of this species and from these measurements (-2268.0 ± 0.9 and 103.6 ± 2.9 kJ · mol^{-1}) derived the standard enthalpies of formation of solid and gas phase to be -271.2 ± 1.1 and -167.6 ± 3.1 kJ · mol^{-1}. Three years later [8] independently determined the former quantity as the numerically incompatible (-327.8 ± 1.1) kJ · mol^{-1} derived from the incompatible measured combustion value of (-2211.4 ± 0.9) kJ · mol^{-1}. The corresponding gas phase value was not discussed (in fact, the aforementioned values were not mentioned) – accepting the enthalpy of sublimation from reference [7] results in (-224.2 ± 3.1) kJ · mol^{-1} for an alternative value for the gas phase enthalpy of formation of pyrazine-2-carboxylic acid. The current paper discusses which, if either, value of the gas phase enthalpy of formation of pyrazine-2-carboxylic acid is to be accepted. Our analysis begins with quantum chemical calculations on pyrazine-2-carboxylic acid and related species.

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http://dx.doi.org/10.1016/j.jct.2016.02.004
0021-9614/

2. Computational details

Calculations were performed for three conformers of pyrazine-2-carboxylic acid, and auxiliary molecules used in this work, namely, benzoic acid (two conformers, the H-bonded and the non-H bonded, were studied), benzene and pyrazine, using the G3(MP2)//B3LYP composite method [9]. In this method the geometries are fully optimized at the B3LYP/6-31G(d) level and the stationary points obtained are characterized as minima through frequency calculations at the same level. Then, single point energy calculations are performed at higher levels of theory: QCISD(T)/6-31G(d) and MP2/GTMP2Large. The final absolute G3(MP2)//B3LYP enthalpies, at $T = 298$ K, are obtained correcting the electronic energies by introducing the vibrational, translational, rotational and the pV terms computed at the B3LYP/6-31G(d) level. Calculations were performed with the Gaussian 03 series of programs [10].

3. Results and discussion

The conformers under consideration for pyrazine-2-carboxylic acid are shown in figure 1. In table 1, we present G3(MP2)//B3LYP calculated absolute and relative enthalpies, at $T = 298$ K, for the three conformers of pyrazine-2-carboxylic acid. Also presented are entropy values and relative Gibbs energies, at $T = 298$ K. As can be seen from this table the calculations predict the conformer with an N···H–O hydrogen bond to be the most stable. The conformational composition, x_i, of each conformer i, in the gas phase, at $T = 298$ K, was calculated through equation (1):

$$x_i = \frac{e^{-\left[\frac{\Delta G^{\circ}_{rel}(i)}{RT}\right]}}{\sum_{i=1}^{n} e^{-\left[\frac{\Delta G^{\circ}_{rel}(i)}{RT}\right]}} \quad (1)$$

To estimate the standard molar enthalpy of formation of each pyrazine-2-carboxylic acid conformer from the respective absolute enthalpy, at $T = 298$ K, we have considered the following homodesmotic reaction:

pyrazine-2-carboxylic acid + benzene → benzoic acid + pyrazine (2)

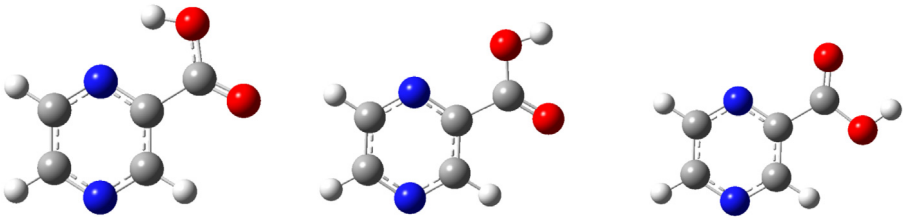
This reaction was chosen to be homodesmotic (there is a balancing in hybridization in addition to conservation of bond types) thus presumably leading to cancelation of most of the correlation energy errors inherent in quantum chemical calculations. Also, gas-phase enthalpies of formation, at $T = 298$ K, of the auxiliary molecules used in reaction (2) are well established experimentally: benzene, (82.6 ± 0.7) kJ · mol^{-1} [11]; benzoic acid, (-294.0 ± 2.2) kJ · mol^{-1} [11]; pyrazine, (203.2 ± 1.5) kJ · mol^{-1} [12].

Combining the calculated reaction enthalpy for each conformer with the experimental values for the auxiliary molecules, we were able to estimate the standard molar enthalpy of formation of each conformer in the gas phase, at $T = 298$ K. Results are presented in table 1. The enthalpy of formation of pyrazine-2-carboxylic acid in the gas phase, at $T = 298$ K, was calculated using the following equation:

$$\Delta_f H^{o}_{298\ K} = \sum_{i=1}^{n} x_i \Delta_f H^{o}_{m}(i) \quad (3)$$

and the derived value is -168.0 kJ · mol^{-1}.

It is found that the experimentally determined enthalpy of formation of pyrazine-2-carboxylic acid as measured by [7] is in nearly perfect agreement with that of the current study. Conversely, it is about (60 kJ · mol^{-1}) different from that value derived from the enthalpy of formation study in [8] and the enthalpy of sublimation study [7]. As such, we recommend the thermochemical values from [7]. Some literature values of other species are impacted by our analysis. The first set of species is made up of other mono-substituted derivatives of pyrazine and the corresponding pyridines. Returning to the analysis in [7], we find the values of the enthalpy of formation of these pyrazine derivatives were compared to that of pyrazine, a value taken from [13]. Recall earlier in our analysis, we used a more recent value [12] that is *ca.* 7 kJ · mol^{-1} less negative than the archival value derived from this source [11]. It was earlier asserted [7] that "increments for pyrazine point for a lower stabilization for about (16 to 20) kJ · mol^{-1}, in comparison with the same substitution on the pyridinic ring".



(I) **(II)** **(III)**

FIGURE 1. B3LYP/6-31G(d) optimized geometries of the three conformers of pyrazine-2-carboxylic acid.

TABLE 1
G3(MP2)//B3LYP results for pyrazine-2-carboxylic acid conformers and auxiliary molecules used in this work.

Conformer/auxiliary molecule	H_{298K}/Hartree	ΔH_{rel}/kJ · mol^{-1}	S°/J · K^{-1} · mol^{-1}	ΔG^{o}_{rel}/kJ · mol^{-1}	x_i	$\Delta_f H^{o}_{298K}$(g)/kJ · mol^{-1}
Pyrazine-2-carboxylic acid (I)	−452.281447	0.0	349.94	0.0	0.9574	−168.49
Pyrazine-2-carboxylic acid (II)	−452.277704	9.8	355.18	8.3	0.0341	−158.66
Pyrazine-2-carboxylic acid (III)	−452.276158	13.9	357.17	11.7	0.0084	−154.60
Benzoic acid (I) (H-bonded)	−420.210276	0.0	356.21	0.0	0.9999	
Benzoic acid (II) (non H-bonded)	−420.201053	24.2	357.81	23.7	0.0001	
Pyrazine	−263.908215					
Benzene	−231.835172					

This discrepancy was left unexplained. Using the new value for the enthalpy of formation of pyrazine reduces the discrepancy to *ca.* ($10\ kJ \cdot mol^{-1}$) which is still larger than expected, or desirable, but at least it is considerably more acceptable. We also note that there are no comparable thermochemical data, neither experimental nor by calculations, on related substituted pyridazines (2 isomers) and pyrimidines (3 isomers) and so the effect of two nitrogen atoms instead of one on the thermochemistry of azine derivatives remains unknown.

The second set of species with affected enthalpies of formation is composed of diverse salts of pyrazine-2-carboxylic acid. The authors of reference [8] published a set of papers on the thermochemistry of these metal-containing species. These involved enthalpies of formation and heat capacities, *e.g.* that of Na^+ [14] and Cr^{3+} [15]. As the former quantity involves both solution phase reaction and combustion calorimetry of solid pyrazine-2-carboxylic acid, a new value for the solid phase enthalpy of formation of this species necessarily affects that of these and other metal salts.

Acknowledgements

We acknowledge these dedicated, courageous and unrealized efforts by Prof. Spoerri as laboratory instructor resulted in an early confirmation to JFL that he should be a theorist. The authors thereby wish to thank Prof. Spoerri and dedicate the current paper to him. D.J.R. Duarte gratefully acknowledges the Secretaría de Ciencia y Tecnología de la Universidad Nacional del Nordeste (SECYT UNNE).

Appendix A

Some decades after the synthesis of pyrazine-2-carboxylic acid, Prof. Spoerri attempted to transform one of the authors (JFL) of this current paper into an experimental chemist [16].

References

[1] S. Gabriel, A. Sonn, Ber. Deut. Chem. Ges. 40 (1908) 4850–4860.
[2] S.A. Hall, P.E. Spoerri, J. Am. Chem. Soc. 62 (1940) 664–665.
[3] P.E. Spoerri, A. Erickson, J. Am. Chem. Soc. 60 (1938) 400–402.
[4] L. Zhang, L. Zhao, Z. Lang, P. Zhang, C. Wang, S.-W. Yuan, J. Tang, Inorg. Chem. 54 (2015) 11535–11541.
[5] M. Stehr, A.A. Elamin, M. Singh, Expert Rev. Anti-Infective Therapy 13 (2015) 593–603.
[6] P.J. Durham, Y. Zhang, N. German, N. Mortensen, J. Dhillon, D.A. Mitchison, P.B. Fourie, A.J. Hickey, Mol. Pharm. 12 (2015) 2574–2581.
[7] M.D.M.C. Ribeiro da Silva, M.S. Miranda, C.M.V. Vaz, M.A.R. Matos, W.E. Acree Jr., J. Chem. Thermodyn. 37 (2007) 49–53.
[8] Y.-X. Kong, Y.-U. Di, W.-W. Yang, S.-L. Gai, Z.-C. Tan, Acta Chim. Sloven. 57 (2010) 370–375.
[9] A.G. Baboul, L.A. Curtiss, P.C. Redfern, K. Raghavachari, J. Chem. Phys. 110 (1999) 7650–7657.
[10] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H. P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision C.01, Gaussian Inc, Wallingford CT, 2004.
[11] J.B. Pedley, Thermochemical Data and Structures of Organic Compounds, TRC Data Series, College Station, Texas, 1994, vol. 1, pp. 1–571.
[12] S.P. Verevkin, V.N. Emel'yanenko, R. Notario, M.V. Roux, J.S. Chickos, J.F. Liebman, J. Phys. Chem. Lett. 3 (2012) 3454–3459.
[13] J. Tjebbes, Acta Chem. Scand. 16 (1962) 916–921.
[14] B. Li, Y.H. Zhang, Y.X. Kong, Y.Y. Di, J.M. Dou, J. Therm. Anal. Calorim. 129 (2015) 1027–1034.
[15] S. Gao, S. Zhang, S. Chen, D. Yang, Thermochim. Acta 543 (2012) 118–124.
[16] I.J. Krems, P.E. Spoerri coauthored an early seminal review of the chemistry of pyrazines, Chem. Rev. 40 (1947) 279–358. A copy of this paper was inscribed by Prof. Spoerri "in the hopes of turning Joel into a good experimental chemist" (1963, trusting JFL's memory of the year to be correct).

JCT 16-89